Author Response

Reviewer 1

1. Well done post hoc analysis of the Emax trial which addresses an important clinical question of time to maximal response to dual bronchodilator therapy. It also reinforces that in addition to higher improvement in lung function that has been demonstrated by multiple studies, clinical improvement is also better with dual therapy. It also demonstrates that improvement is not universal and that some patients do not show improvement - this may in part be due to pre-existing therapy prior to randomization as about two thirds of the patients were on a bronchodilator during run in. Although not mentioned in the table, I assume they mean a long acting bronchodilator and if that is the case, I would clarify that in the table.

Author response

We thank the reviewer for their comments. We have amended Table 1 to clarify that the use of a bronchodilator during run-in refers to a long-acting bronchodilator.

2. The potential of a blunted reponse in patients on long acting bronchodilators is mentioned in the discussion. It would be interesting to look at response in patients not on any long acting therapy prior to randomization, as the physiologic response would be expected to be greater in that group, and see if there is a corresponding clinical response. Overall, i think this is a well done manuscript and would endorse its publication.

Author response

We agree that it is important to investigate the treatment response in patients who were not receiving a longacting bronchodilator prior to randomisation and we have previously presented an abstract on this subgroup of patients in the EMAX study (Bjermer L et al. Am J Respir Crit Care Med. 2019;199:A3317). Due to the substantial amount of data and the importance of this subgroup, we are currently preparing a separate manuscript focusing on this subgroup of patients. For this reason, we have not included these data in this manuscript.

Reviewer 2

1. This is a well-written manuscript. The manuscript's topic is relevant. Page 12, line 39-45: the authors should assess the relationship between ERS:COPD total score and sub-domains and rescue medication use. This would clarify the potential utility of rescue medication use as an indicator of symptom control in patients with COPD.

Author response

We thank the reviewer for their comments and agree that the relationship between E-RS:COPD and rescue medication is of interest; however, the relationship is complex and would require detailed description, which is out of scope for this manuscript. We have previously presented an abstract on this subject (Maltais F et al. Eur Respir J. 2019;54(suppl 63):OA2108) and are currently preparing a separate manuscript that will provide a detailed

analysis. The Discussion has been amended to note this analysis, *"However, another prospective analysis of the EMAX trial suggests that the relationship is complex and ~~This association~~ warrants further investigation. ~~as rescue medication could be considered a useful indicator of symptom control in patients with COPD, as has been shown in patients with asthma.~~"*

2. Another study limitation should be mentioned: the EMAX study is a 24-week study, while maintenance pharmacological treatment of patients with COPD is expected to last longer than that. Result interpretation should be limited to this time frame.

Author response

We have added the following sentence to the Discussion to note this limitation, *"The EMAX study was 24 weeks in duration; longer-term studies are required to determine whether the responses measured at the end of this study are sustained for longer treatment durations."*

3. In the introduction, I would suggest to mention the mechanistic basis of the greater bronchodilating effect of umeclidinium/vilanterol fixed dose combination as comparer with either bronchodilator alone (Ther Adv Respir Dis 2018;12:1753466618760779).

Author response

A sentence has been added to the Introduction to note the complementary mechanisms of action of LAMAs and LABAs, *"Due to their differing mechanisms of action, combining a LAMA (which mediates bronchodilation through antagonism of muscarinic acetylcholine M3 receptors) with a LABA (which mediates bronchodilation through activation of β2-adrenoceptors) maximises bronchodilation with greater efficacy than either monotherapy alone. ~~with~~ Therefore, LAMA/LABA dual therapy is considered ~~to be~~ appropriate in patients who experience severe breathlessness or have a high risk of exacerbations."*